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International application No. <b>PCT/US96/20577</b>	Applicant's or agent's file reference <b>19191.0001/P</b>
International filing date (day/month/year) <b>19 December 1996 (19.12.96)</b>	Priority date (day/month/year) <b>21 December 1995 (21.12.95)</b>
<b>Applicant</b> <b>MADISON, Edwin, L. et al</b>	

1. The designated Office is hereby notified of its election made:

 in the demand filed with the International Preliminary Examining Authority on:**21 July 1997 (21.07.97)** in a notice effecting later election filed with the International Bureau on:2. The election  was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>C07K 1/00, 14/00, 16/00, 17/00, C12P 21/02, 21/04, 21/08, A61K 39/395, 39/40, 39/42, 38/00, G01N 33/53</b>		A1	(11) International Publication Number: <b>WO 97/39021</b> (43) International Publication Date: <b>23 October 1997 (23.10.97)</b>
(21) International Application Number: <b>PCT/US96/20577</b> (22) International Filing Date: <b>19 December 1996 (19.12.96)</b>		(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(30) Priority Data: <b>60/009,028 21 December 1995 (21.12.95) US</b>		Published <i>With international search report.</i>	
(71) Applicant ( <i>for all designated States except US</i> ): THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US).			
(72) Inventors; and (75) Inventors/Applicants ( <i>for US only</i> ): MADISON, Edwin, L. [US/US]; 615 Stratford Court #3, Del Mar, CA 92014 (US). SMITH, Jeffrey, W. [US/US]; 12602-6 Carmel Country Road, San Diego, CA 92130 (US).			
(74) Agents: SELBY, Elizabeth et al.; Needle & Rosenberg, Suite 1200, 127 Peachtree Street, N.E., Atlanta, GA 30303 (US).			

(54) Title: TARGETED THERAPEUTIC OR DIAGNOSTIC AGENTS AND METHODS OF MAKING AND USING SAME

(57) Abstract

The present invention provides a targeted therapeutic or diagnostic agent comprising (a) a therapeutic or diagnostic functional entity linked to one of the following: (a) an isolated peptide mimetic that specifically binds a selected target; (b) an isolated, optimized, high-affinity polyamino acid that specifically binds a selected target; (c) an isolated protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the functional entity. The invention additionally provides methods of targeting therapeutic or diagnostic agents to a target. Additionally provided is a method of targeting a therapeutic agent to a platelet using the present agents, and methods of treating diseases and disorders associated with blood clots. Specifically provided is a recombinant targeting protein wherein the surface loop is the HCDR3 of monoclonal antibody Fab-9, the second protein is human tissue type plasminogen activator (t-PA), and the target is platelet glycoprotein GPIIb/IIIa (integrin  $\alpha$ IIb $\beta$ I).

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## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D 15 APR 1998  
WIPO PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 19191.0001/P	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US96/20577	International filing date (day/month/year) 19 DECEMBER 1996	Priority date (day/month/year) 21 DECEMBER 1995
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE SCRIPPS RESEARCH INSTITUTE		

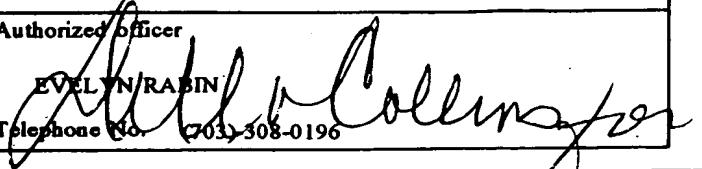
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of \_\_\_\_\_ sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 21 JULY 1997	Date of completion of this report 24 MARCH 1998
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN RABIN Telephone No. (703) 308-0196 

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/20577

**L Basis of the report**

1. This report has been drawn on the basis of (Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments).

 the international application as originally filed. the description, pages 1-42 \_\_\_\_\_, as originally filed.pages NONE \_\_\_\_\_, filed with the demand.pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

 the claims, Nos. 1-55 \_\_\_\_\_, as originally filed.Nos. NONE \_\_\_\_\_, as amended under Article 19.Nos. NONE \_\_\_\_\_, filed with the demand.Nos. NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_

 the drawings, sheets/fig 1-4 \_\_\_\_\_, as originally filed.sheets/fig NONE \_\_\_\_\_, filed with the demand.sheets/fig NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_

2. The amendments have resulted in the cancellation of:

 the description, pages NONE \_\_\_\_\_. the claims, Nos. NONE \_\_\_\_\_. the drawings, sheets/fig NONE \_\_\_\_\_.

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/20577

**V. Reasons and statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-55</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-55</u>	NO
Industrial Applicability (IA)	Claims <u>1-55</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-55 lack an inventive step under PCT Article 33(3) as being obvious over Backstrom *et al.* [Gene 165: 163-171 (Jan 1995)] in view of Allaway *et al.* [WO 94/19017 (Sept 1994)], Capon *et al.* [U.S. Patent 5,359,046 (Oct 1994)], Shin, S-U. [Biotherapy 3: 43-53 (1991)], Shin *et al.* [J. Biol. Chem. 269: 4979-4985 (Feb 1994)], Bei *et al.* [J. Immunol. Methods 186: 245-255 (1995)], Cheon *et al.* [Proc. Natl. Acad. Sci. USA 91: 989-993 (Feb 1994)], de Lorimier *et al.* [Biochem. 33: 2055-2062 (1994)], Duarte *et al.* [AIDS Research and Human Retroviruses 10: 235-239 (1994)], and Hearst *et al.* [Prot. Engineer. 7: 1411-1421 (1994)]. Backstrom *et al.* teach hybrid proteins wherein viral epitopes are inserted into cholera toxin subunit carrier proteins as an aid to targeting. Allaway *et al.*, Capon *et al.*, Shin, S-U., Shin *et al.*, Bei *et al.*, Cheon *et al.*, de Lorimier *et al.*, Duarte *et al.*, and Hearst *et al.* teach the selection of particular epitopes to be "fused" and methods of making and using fusion proteins for therapeutic and diagnostic purposes. It would have been obvious to combine the teachings of Backstrom *et al.* with those of Allaway *et al.*, Capon *et al.*, Shin, S-U., Shin *et al.*, Bei *et al.*, Cheon *et al.*, de Lorimier *et al.*, Duarte *et al.*, and Hearst *et al.* in order to make the many therapeutic and diagnostic reagents encompassed by the claims.

**----- NEW CITATIONS -----**

NONE

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/20577
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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 387.3, 388.25, 388.7; 424/133.1, 145.1, 152.1, 159.1; 514/12; 435/7.1, 69.5, 69.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, CAPLUS, WPIDS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/19017 (A1 PROGENICS PHARMACEUTICALS, INC.) 01 September 1994 (01.09.94), see entire document.	1-55
Y	US 5,359,046 A (CAPON et al.) 25 October 1994, see entire document.	1-55
Y	SHIN. Chimeric Antibody: Potential Applications for Drug Delivery and Immunotherapy. Biotherapy, 1991, Vol. 3, pages 43-53, see entire document.	1-55
Y	SHIN et al. Functional Properties of Antibody Insulin-like Growth Factor Fusion Proteins. The Journal of Biological Chemistry. 18 February 1994, Vol. 269, No. 7, pages 4979-4985, see entire document.	1-55

 Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

07 APRIL 1997

Date of mailing of the international search report

27 MAY 1997

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Washington, D.C. 20231Authorized officer *IW for*  
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Facsimile No. (703) 305-3230

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/20577
---

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BEI et al. Baculovirus Expression of a Functional Single-chain Immunoglobulin and Its IL-2 Fusion Protein. Journal of Immunological Methods. 26 October 1995, Vol. 186, pages 245-255, see entire document.	1-55
Y	CHEON et al. High-affinity Binding Sites for Related Fibroblast Growth Factor Ligands Reside Within Different Receptor Immunoglobulin-like Domains. Proc. Natl. Acad. Sci. USA. February 1994, Vol. 91, pages 989-993, see entire document.	1-55
Y	BACKSTROM et al. Characterization of an Internal Permissive Site in the Cholera Toxin B-subunit and Insertion of Epitopes from Human Immunodeficiency Virus-1, Hepatitis B Virus and Enterotoxigenic Escherichia coli. Gene. Vol. 165, pages 163-171, see entire document.	1-55
Y	DE LORIMIER et al. NMR-Derived Solution Conformations of a Hybrid Synthetic Peptide Containing Multiple Epitopes of Envelope Protein gp120 from the RF Strain of Human Immunodeficiency Virus. Biochemistry. March 1994, Vol. 33, pages 2055-2062, see entire document.	1-55
Y	DUARTE et al. Multiepitope Polypeptide of the HIV-1 Envelope Induces Neutralizing Monoclonal Antibodies against V3 Loop. AIDS Research and Human Retroviruses, 1994, Vol. 10, No. 3, pages 235-243, see entire document.	1-55
Y	HEARST et al. GRAFTER: a Computational Aid for the Design of Novel Proteins. Protein Engineering, 1994, Vol. 7, No. 12, pages 1411-1421, see entire document.	1-55

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US96/20577

**A. CLASSIFICATION OF SUBJECT MATTER:**  
IPC (6):

C07K 1/00, 14/00, 16/00, 17/00; C12P 21/02, 21/04, 21/08; A61K 39/395, 39/40, 39/42, 38/00; G01N 33/53

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US CL :

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